REMARKS/ARGUMENTS

The Office Action mailed June 30, 2005 has been carefully reviewed and the foregoing amendments are made in response thereto. Claim 1 is amended to correct antecedent basis errors in response to the Examiner's comments as described in more detail below. In view of the amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Rejections under 35 U.S.C. § 112 should be withdrawn.

Claims 1-6 and 10-29 are rejected because the phrase "said array" in claim 1 lacks antecedent basis. Claim 1 has been amended to provide antecedent basis for the term "said array".

Rejections under 35 U.S.C. § 103 should be withdrawn.

Claims 1-4, 6, and 10-29 stand rejected as allegedly being obvious over Lockhart *et al.* (US Patent No. 6,040,138), in view of Pharmacia Biotech (Molecular and Cell Biology Product Catalog, 1994) [Pharmacia], and Williams *et al.* (Nucleic Acids Research, Vol. 22, pages 1365-1367, 1994), and further in view of Stahl *et al.* (The Journal of Histochemistry and Cytology, Vol. 41, pages 1735-1740, 1993). This rejection is respectfully traversed.

Lockhart *et al.* is cited as discussing methods of monitoring gene expression by hybridization of cDNAs derived from total RNA or mRNAs by reverse transcription using oligo dT primers to high density oligonucleotide arrays. Pharmacia is cited as discussing the use of random primers for making cDNA from RNA. Williams et al. is cited as discussing the unpredictable effect on duplex stability resulting from dangling

ends in a duplex formed by the hybridization of two oligonucleotides. Stahl et al. is cited as discussing methods for selection of oligonucleotide probes for the detection of mRNA isoforms.

The Examiner asserts that it would have been obvious to modify the method of Lockhart *et al.* to use the random primers of Pharmacia, that one of skill in the art would have been motivated by Williams *et al.* to fragment the resulting cDNA and by Stahl *et al.* to provide isoform-specific probes.

The Examiner takes the view that one of skill in the art would have been motivated by Williams *et al.* [Williams] to modify the method of Lockhart *et al.* by fragmenting the cDNAs before labeling in order to minimize the occurrence of dangling ends to achieve "better consistency" in the signal intensities (presumably from probe to probe within a single array). Applicants respectfully disagree with this characterization of the results shown in Williams and suggest that one of skill would not interpret the results shown in Williams to be broadly applicable to all duplex interactions and would not be motivated by Williams to fragment cDNA prior to hybridization to an array.

Williams shows the hybridization of a single 10 base target to a plurality of 10 base probes of varying sequence. The probes hybridized to the target with different degrees of complementarity (7 to 10 contiguous bases) generating overhangs of between 0 and 3 bases on either the 5' or 3' end of the target. As the overhang increases, the length of the duplex decreases from 10 to 7 base pairs. Williams observed that when this target hybridized to a probe with 8 base pairs of complementarity and a 2 base overhang the hybridization intensity was unexpectedly greater than when the target hybridized to a different probe with 9 base pairs of complementarity and a 1 base overhang. This

stabilizing effect of the 2 base overhang compared to the 1 base overhang was seen with only with a GA overhang at the 5' end of the target-GA was the only two base 5' overhang tested. A 3' overhang of CA showed no effect on hybridization. In no case did they observe a destabilizing effect of an overhang and most of the overhangs tested had no effect (Fig. 1).

It is not clear to what extent these limited observations using a single target and simultaneously varying probe sequence and number of base pairs in the duplex should be applied to other targets and other probe lengths. It is well known in the art that different probe sequences hybridize with different affinities to their respective targets. As a result it is less important to have consistent signal intensity from probe to probe than to have consistent hybridization to the same probe from sample to sample, for example, from array to array. It is also not clear from Williams that the variations observed are due to the overhang and not to the specific sequence of the overhang. In the abstract (p1365) they state that "it is not clear whether this is due to the orientation of the overhang or the effect of specific bases."

Assuming *arguendo* that Williams suggests that eliminating overhangs is advantageous, fragmenting a population of cDNA as taught in the present application would not be expected to generate the uniformly sized fragments necessary to eliminate overhangs. To eliminate overhangs the target fragments should be identical in length to the probe and perfectly complementary. This would require sequence specific fragmentation and fragmentation to a specified length, for example, if the probes of the array are 25 bases the fragments should also be 25 bases. Fragmentation by a non-sequence specific nuclease such as the DNase I method disclosed on page 22, lines 4-5,

of the specification would not result in the defined fragment sizes required to achieve the consistency suggested by the Examiner. Instead such fragmentation results in fragments that are a variety of sizes within a range of sizes, preferably 30 to 150 bases, as disclosed on page 22, line 5 of the specification.

Claim 5 is rejected under 35 U.S.C. §103(a) over Lockhart in view of Pharmacia, Williams *et al.*, Stahl *et al.* and further in view of the Gibco BRL Catalog. Claim 5 is nonobvious for at least the same reasons as claim 1.

In summary, since the cited references, alone or in combination, do not teach or suggest the presently claimed invention, Applicants respectfully submit that the rejection of claims 1-6 and 10-29 under 35 U.S.C. §103(a) should be withdrawn.

CONCLUSION

If the Examiner has any questions pertaining to this application or feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5000.

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Respectfully submitted,

Sandra E. Wells
Reg. No. 52,349

Customer No.: 22886
Legal Department
Affymetrix, Inc.
3380 Central Expressway
Santa Clara, CA 95051
Tel: 408/731-5000
Fax: 408/731-5392